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Serial No.: 09/720,762 Confirmation No.: 5214
Applicant: Yanase, et al.
Title: GASKET WITH TAPERED SLANT FOR USE IN A PRE-FILLED SYRINGE
AND PRE-FILLED SYRINGE
Filed: December 28, 2000 Art Unit: 3746
Atty Docket: 114474.00014 Examiner: Hamo, Patrick

DECLARATION OF KEIZOU NAKAMOTO PURSUANT TO 37 C.F.R. § 1.132

I, Keizou Nakamoto, declare that:

1. I currently reside in Saitama, Japan, and make this declaration of my own knowledge and belief.
2. I am a Researcher Superintendent at EISAI, Co., Ltd, and have held this position for the past six years. Prior to my current position, I worked as a researcher for EISAI for 12 years. During my 18 years of employment with EISAI I have conducted research in the fields of injection agent technology and drug technology of solid drugs. Prior to my employment at EISAI, I received a master's degree in chemical engineering from Nagoya University in 1992.
3. I am a co-inventor of U.S. Patent Application No. 09/720,762 ("the '762 application") and am familiar with the subject matter of the application and what would have been known in the art at the time of the invention.
4. I have carefully read the February 12, 2010 Office Action issued by the Patent Office during prosecution of the '762 application and the references cited therein.
5. In order to address problems identified with previous gaskets, I and four other researchers at EISAI conducted a series of experiments between April 1997 and December

1997 to test syringe gaskets with different characteristics. Six different gasket shapes were developed and tested using Teflon-laminated gaskets made of different materials and JIS hardness.

6. The testing protocol was as follows: Each gasket was tested in a syringe barrel filled with either a contrast medium (IOM 300 mgI) or distilled water and sterilized at 115°C for 60 minutes. After drying, multiple tests were performed on each gasket and syringe, including a set of three tests that checked (1) gasket position; (2) the relative alignment of the gasket within the syringe ("crook"); and (3) the presence or absence of liquid leakage.

7. The gasket position was determined by measuring the distance from a collar surface of the syringe barrel to a gasket screw-side bottom surface using a gasket position inspector, a table-type gasket inspector, or a digital caliper. For 100 mg syringes, gaskets having gasket positions between 7.3 and 11.5 mm were considered acceptable, but gaskets positions measured at less than 7.3 mm were considered to have failed the test. For 50 mg syringes, gasket positions between 69.0 and 74.0 mm were considered acceptable, but positions measured at less than 69.0 mm were considered to have failed the test.

8. The crook of the gasket was determined by measuring the maximum value and the minimum value of the gasket position measurement for each gasket, the difference between these values being defined as the value of the crook. Gaskets having a crook value of 2 mm or less were considered acceptable and those with a value greater than 2 mm were considered to have failed the test.

9. With respect to testing the presence or absence of leakage, it was visually observed whether or not the contrast medium was leaking in a droplet form behind a contact part between the gasket and the syringe barrel. Those gaskets with no observed leakage were

considered acceptable and those with observable liquid leakage were considered to have failed the test.

10. The results of the testing described above are attached as Appendix 1 ("App. 1"). The first set of testing (Table 1) shows the test results of the six different shapes of gaskets ("A" to "F") having a JIS hardness of 48-51. The second set of testing (Table 2) used gaskets made of a different material with a similar hardness. The third set of testing (Table 3) used gaskets made of a third material but having a hardness of JIS 57-60. The fourth set of testing (Table 4) was limited to the two shapes of gaskets that showed the best results from the first three tests and having a JIS hardness of 57-59, but varying whether the liquid contact portion of the gasket was treated with silicone ("B2-41") or not ("B2-01").

11. From the four sets of testing, a final gasket type was selected: the "E" shape (which is shaped in accordance with the present invention) having a JIS hardness of 57-60. The fifth set of test results (Table 8) show the results of testing this selected gasket in both 100 mg and 50 mg syringes.

12. Below is a comparison of the testing results of the selected gasket shape made of D21-5-1 rubber, with one set of gaskets having a JIS hardness of 48-51 and the second set having a JIS hardness of 57-60. (See App. 1, Table 1 and Table 8.)

Comparison of Test Results
Gasket Shape: EP-15-E
Gasket Material: D21-5-1

Test No.	JIS Hardness	No. Gaskets Tested	Gasket Position Test		Crook Test		Leakage Test	
			Number Rejected	%	Number Rejected	%	Number Rejected	%
1	48-51	198	98	49.5	2	1.0	51	25.8
5	57-60	190 ¹	0	0	0	0	0	0

¹ Includes both 100 mg and 50 mg test results from Table 8.

13. As shown above, almost half (49.5%) of the gaskets with a JIS hardness of 48-51 were rejected for failing the position test, 1% failed the crook test, and 25.8% failed the leakage test. It was observed that many of the gaskets failed due to leakage or the changing of the gasket position within the syringe (leading to failure of the gasket position and/or the crook test) that occurred during the sterilization process.

14. In contrast, none of the gaskets in the final testing with a JIS hardness of 57-60 were rejected for failing the gasket position, crook or leakage tests. This is consistent with the other sets of testing performed, which also showed that an increase in JIS hardness to the range of 57-60 drastically reduced or eliminated testing failures due to gasket position, crook or leakage. Such a dramatic improvement was surprising and unexpected to me and my fellow researchers who performed the experiment.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Subject Application or any patent which issues thereon.

Signed on this 3 th day of August 2010.

Keizou Nakamoto
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APPENDIX 1

Table. 1 Effect of gasket type, material and hardness (EP-15-A~F, B2-00)

Gasket Material : D21-5-1 Hardness : 48-51
 Filling fluid : 10N300mg! Volume : 102ml

LOT NO	Type of gasket	Number of Sample	Reason of Rejection	Number	%	Gasket MN	Crack [m]	MAX	Average	StdDev	Number	%	Drop Out
Gasket LOT NO				1)	2)								
37042201	EP-15-A 970137	197	Abnormal position	49	24.8								
			Crooked gasket	16	8.1	9.14	0.31	3.58	1.75	0.31	-	-	-
37042202	EP-15-B 970138	198	Abnormal position	96	48.4								
			Crooked gasket	25	12.6	9.68	0.48	3.91	2.04	0.48	44	22.2	Drop Out
37042203	EP-15-C 970139	198	Abnormal position	105	53.5								
			Crooked gasket	25	12.6	9.70	0.33	7.59	2.04	0.33	32	16.2	Drop Out
37042204	EP-15-D 970140	198	Abnormal position	77	38.9								
			Crooked gasket	0	0.0	10.15	0.33	2.77	1.10	0.33	76	38.3	Drop Out
37042205	EP-15-E 970141	198	Abnormal position	98	49.5								
			Crooked gasket	2	1.0	10.23	0.38	2.92	1.33	0.36	51	25.6	Drop Out
37042206	EP-15-F 970142	198	Abnormal position	110	55.6								
			Crooked gasket	0	0.0	10.41	0.33	2.62	1.19	0.33	99	50.0	Drop Out

1) Abnormal position : less than 7.3 mm of total length between tail of barrel position and gasket's bottom position
 2) Crooked gasket : OK \leq 2mm , NG $>$ 2mm

Table 2 Effect of gasket type, material and hardness (EP-15-A~F, B2~41)

LOT NO	Type of gasket	Number of Sample	Reason of Rejection	Number	gasket MIN	gasket MAX	Crock [mm]	Drop test	Number %		
									MIN	Average	
37072301	EP-15-A	19	Abnormal position	4	21.1				0.50	2.19	
			Crooked gasket	14	73.7	6.63	0.50	No Detect			
		Total		14	73.7						
37072302	EP-15-B	20	Abnormal position	1	5.0				0.01	1.64	
			Crooked gasket	4	29.0	7.05	0.01	No Detect			
		Total		4	29.0						
37072303	EP-15-C	20	Abnormal position	2	10.0				0.33	0.96	
			Crooked gasket	3	15.0	7.05	0.33	No Detect			
		Total		3	15.0						
37072304	EP-15-D	20	Abnormal position	0	0.0				0.19	1.25	
			Crooked gasket	0	0.0	7.86	0.19	No Detect			
		Total		0	0.0						
37072305	EP-15-E	20	Abnormal position	0	0.0				0.13	0.34	
			Crooked gasket	0	0.0	0.07	0.13	No Detect			
		Total		0	0.0						
37072306	EP-15-F	20	Abnormal position	0	0.0				0.12	0.30	
			Crooked gasket	0	0.0	8.24	0.05	No Detect			
		Total		0	0.0						
1) Abnormal position : less than 7.3 mm of total length between tail of barrel position and gasket's bottom position											
2) Crooked gasket : OK \leq 2mm , NG > 2mm											

Table 3 Effect of gasket type, material and hardness (EP-15-A~F, B2-41)
 Gasket Mater [a] : D21-6-1 Hardness : 57-60
 Filling fluid : WFI Volume : 102ml

LOT NO	Type of gasket	Number of Sample	Reason of Rejection	Number	Gasket Position		Crock [mm]	Drop test
					MIN	MAX		
37072401	EP-15-A	20	Abnormal position	0	0.0		0.63	0.26
			Crooked gasket	0	0.0	7.83		
		Total		0	0.0			
37072402	EP-15-B	20	Abnormal position	0	0.0		0.63	0.18
			Crooked gasket	0	0.0	7.97		
		Total		0	0.0			
37072403	EP-15-C	20	Abnormal position	0	0.0		0.57	0.24
			Crooked gasket	0	0.0	9.11		
		Total		0	0.0			
37072404	EP-15-D	20	Abnormal position	0	0.0		0.03	0.25
			Crooked gasket	0	0.0	9.65		
		Total		0	0.0			
37072405	EP-15-E	20	Abnormal position	0	0.0		0.49	0.16
			Crooked gasket	0	0.0	8.57		
		Total		0	0.0			
37072406	EP-15-F	20	Abnormal position	0	0.0		0.44	0.10
			Crooked gasket	0	0.0	8.78		
		Total		0	0.0			

1) Abnormal position : less than 7.3 mm of total length between tail of barrel position and gasket's bottom position
 2) Crooked gasket : OK ≤2mm , NG > 2mm

Table 4 Effect of gasket type, material and hardness (EP-15-E, F B2-01-B2-41)
Gasket Material : D21-5-1 Hardness UP Hardness : 57-59
Filling fluid : WFI and OM300Omg/L Volume : 102ml

LOT NO	Type of gasket	Number of Sample	Reason of Rejection	Number	Abnormal position	Crock [mm]		Droplet	
						MIN	MAX	Average	StdDev
(108300)	EP-15-E		Abnormal position	0	0.0				
	970651	40	Crooked gasket	0	0.0	8.01	0.33	1.03	0.61
	B2-41		Total	0	0.0				
(108300)	EP-15-E		Abnormal position	0	0.0				
	970646	99	Crooked gasket	0	0.0	7.78	0.04	0.92	0.38
	B2-01		Total	0	0.0				
(108300)	EP-15-E		Abnormal position	0	0.0				
	970640	89	Crooked gasket	0	0.0	8.26	0.10	1.14	0.41
	B2-41		Total	0	0.0				
(108300)	EP-15-F		Abnormal position	0	0.0				
	970652	40	Crooked gasket	0	0.0				
	B2-41		Total	0	0.0				
(108300)	EP-15-F		Abnormal position	0	0.0				
	970647	100	Crooked gasket	0	0.0	7.73	0.31	1.07	0.60
	B2-01		Total	0	0.0				
(108300)	EP-15-F		Abnormal position	0	0.0				
	970641	100	Crooked gasket	0	0.0	7.89	0.11	1.04	0.45
	B2-41		Total	0	0.0				
(108300)	EP-15-F		Abnormal position	0	0.0				
	970641	100	Crooked gasket	0	0.0	8.34	0.12	0.99	0.44
(108300)	B2-41		Total	0	0.0				
	1) Abnormal position : less than 7.3 mm of total length between tail of barrel position and gasket's bottom position 2) Crooked gasket : OK ≤2mm , NG > 2mm								

Table.8 Evaluation of gasket position, crook and droplet in 104300S-100, 50
 Gasket Material : D21-5-1 Hardness : 57-60

LOT No	Type of Gasket	Number of Samples	Reason of Rejection	Number	Position	Gasket		Crock [ml]	MAX	Average	StdDev	Number	Droplet %
						MIN	MAX						
104300-100	EP-15-E	82-01	Abnormal position	0	0.0								
		970689	Crooked gasket	0	0.0	7.05	0.07						
			Total	0	0.0								
104300-50	EP-15-E	82-01	Abnormal position	0	0.0								
		970772	Crooked gasket	0	0.0	71.05	0.04						
			Total	0	0.0								

- 1) 100m| Abnormal position : less than 7.3 mm of total length between tails of barrel position and gasket's bottom position
 2) 50m| Abnormal position : less than 69.00 mm of total length between tails of barrel position and gasket's bottom position
 3) Crooked gasket : OK \leq 2mm , NG > 2mm